REMARKS

This supplemental amendment has been prepared and filed in response to the Examiner's Interview held October 26, 2004. It is an addition or supplemental with respect to the amendment filed August 31, 2004.

Claims 32 to 38 and 45 to 51 were rejected as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (based on English CAPLUS Abstract).

1. English Translation of KR 9606729

The current obviousness rejection is based on a combination of the subject matter of Voorspoels, et al, with the KR reference. This KR reference is difficult for the applicants to obtain and only the English language Caplus abstract has been supplied with the Office Action. Consequently applicants respectfully request that the U.S. Patent Office supply a copy of KR 9606729 in the Korean language or an English translation of KR 9606729. The Examiner indicated that she would obtain an English translation of KR 9606729 during the interview held October 26, 2004.

2. Comparative Evidence and Claim Changes

A. Declaration Evidence

A signed copy of the Declaration showing unexpectedly superior performance for the claimed bioadhesive tablets of claim 45 and 49 (which are made by the methods of claim 32 and 36) was filed in the U.S. Patent Office per fax on October 28, 2004. If this signed copy is not available for examination, please let us know by calling the telephone number below.

The results in the signed Declaration were discussed during the interview. The Declaration reports the respective amounts of a testosterone ester, namely testosterone undecanoate, that dissolves in water at body temperature after 2 hours from tablets made by the dry mixing method of Voorspoels, et al, and by the spray-drying method according to the claimed invention. No testosterone undecanoate is present in water at body temperature when the tablet is made by the dry mixing method of Voorspoels, et al. In fact, in general the equilibrium solubilities of testosterone undecanoate would be low because of the lower solubilities of these esters in relation to testosterone itself (see column 1, page 1228, of Voorspoels, et al). However it was surprisingly found that increasing amounts of HPMC in the tablet made by spray drying promoted the solubility of testosterone undecanoate so that a significant amount of this ester was observed to dissolve after two hours at about 0.40 % HPMC. The same solubility promoting action of HPMC was not observed, when the bioadhesive tablet was made by dry

mixing according to the prior art method of Voorspoels, et al. Increasing amounts of HPMC increased the amount of testosterone ester dissolved when the bioadhesive tablets were made with the amorphous premix by spray drying according to the invention.

It should be emphasized that the solubility results in the Declaration are experimental facts and not speculative theories. The Declaration is signed by the inventor and the solubility promoting action of HPMC in the case of the bioadhesive tablet made by spray drying must be accepted as true.

The significance of the solubility experiments reported in the Declaration is that the organic polymer (e. g. HPMC) of claims 32, 36, 45 and 49 will promote the availability of the effective ingredient, the testosterone ester, in the saliva (which is also at body temperature). Then during buccal administration a comparatively much higher super-saturation solubility of testosterone undecanoate is provided at the moist oral mucosa when the bioadhesive tablet according to the claimed invention made by spray drying is used instead of the tablet made by the prior art dry mixing method of Voerspoels, et al.

These experiments show the criticality of forming an amorphous active ingredient premix according to the claimed method instead of a mixture of crystalline testosterone ester as in the case of the prior art method.

The claim changes above have now limited the claims to a premix or tablet containing at least one testosterone ester with or without testosterone itself or to testosterone undecanoate with or without testosterone. The comparative evidence in the Declaration, which is also limited to an ester of testosterone, then

supports a finding that the claimed bioadhesive tablets made by the spray drying technique with formation of an amorphous active ingredient premix are surprisingly more effective because the bioavailability of the testosterone ester is surprisingly greater.

B. Specification

Model experiments in which testosterone alone, testosterone undecanoate and a mixture of testosterone and testosterone undecanoate were administered using bioadhesive tablets made by applicants' claimed methods are reported in applicants' specification. The particular method for making these bioadhesive tablets is described in examples 1 to 3 starting on page 6 of applicants' specification. The testosterone plasma levels results from the buccal administration of these bioadhesive tablets is shown in figs. 1 to 3 of the specification.

It should be pointed out that claims 32 and 45 have now been amended to claim a bioadhesive tablet (or method of making it by spray drying) containing testosterone undecanoate or a mixture of testosterone undecanoate and testosterone. Thus these claims and the claims dependent on them correspond exactly in their scope of the model experimental results shown in figs. 1 to 3 in applicants' specification.

The results of these model experiments are discussed in the last full paragraph on page 5 of the applicants' specification. They clearly show that by a combination of testosterone and a testosterone ester, namely testosterone

undecanoate, it is possible to recreate or simulate the body's own rhythmicity. When testosterone undecanoate is combined with testosterone in a bioadhesive tablet, the testosterone level in the plasma is extended as shown in fig. 3.

However Voorspoels, et al, on page 1228, last line, left column, to first two lines of the right hand column, teach that this cannot be done. The reference states that, "Current therapies are unable to simulate the circadian rhythm of testosterone plasma levels in healthy men (1)." Thus the results regarding testosterone undecanoate in applicants' specification as shown in figs. 1 to 3 are unexpected.

These model administration test results are evidence for the patentability of the method claims in amended claims 32, 34 and 35 and of the bioadhesive tablet claimed in amended claims 45, 47 and 48 above.

Finally, the KR reference -- to the extent known from the CALPUS abstract -- does disclose methods of making a bioadhesive tablet by spray drying a solution of an effective ingredient in general and a polymer, such as hydroxypropyl cellulose, to make a micropellet.

However the KR reference does not explain why one would be motivated to use a more complex spray drying method than dry mixing of a crystalline effective ingredient with the adjuvents and excipients.

One would not be motivated to select the spray drying method given the results of Voorspoels, et al, because this reference teaches that bioadhesive tablets with good adhesive properties can be made by the simpler dry mixing methods using crystalline effective ingredients.

Thus the KR reference would not provide the motivation or suggestion necessary for one skilled in the art to obtain applicants' claimed bioadhesive tablet. Neither reference suggests that the bioadhesive tablets made by the spray drying will provide significantly greater bioavailability of testosterone when a testosterone ester is used to administer testosterone.

Arguments were also filed to overcome the case of *prima facie* obviousness rejection based on a combination of Voorspoels, et al, and the KR reference in the amendment dated August 31, 2004. These arguments were also discussed during the interview and will not be discussed further here.

For the foregoing reasons especially the comparative experimental evidence and because of the changes, withdrawal of the rejection of claims 32, 34, 35, 36, 37 and 38 and 45, 47, 48, 49, 50 and 51 as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (based on English CAPLUS Abstract) is respectfully requested.

The relationship of the disclosures in Timpe, et al, to those of the claimed invention was handled in the accompanying amendment. Briefly, Timpe, et al, would not motivate one skilled in the art to use the spray drying method to make the bioadhesive tablets either.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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